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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/804,409	03/12/2001	Timothy J. Kieffer	029996-0278721	1113

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,409	KIEFFER ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 56-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/4/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 31-55, in Paper No. 15 is acknowledged.

Claims 1-30 and 56-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached **N**otice To Comply With Requirements For Patent Applications Containing **N**ucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. *Any* response to this Office Action, which fails to meet all of these requirements, will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Objections

Claims 38, 41-42, 45-46 and 54 are objected for depending on a non-elected claim.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of treating a subject having, or at risk of having, a disorder treatable by producing a therapeutic protein in a muscosal tissue, comprising contacting muscosal tissue cells in the subject transformed with a polynucleotide comprising an expression control element in operable linkage with a nucleic acid encoding the therapeutic protein with a nutrient that induces production of the protein in an amount effective to treat the disorder, wherein the expression control element comprises a nutrient-regulatable element, and wherein the nutrient regulatable element comprises a gut endocrine promoter, functional variant thereof, or a functional subsequence thereof.

The nucleotide sequences that encode all variants or functional subsequences thereof of gut endocrine promoters, encompassed within the

genus of nucleotide molecules of gut endocrine promoters have not been disclosed. Based upon the prior art there is expected to be variation among the species of DNA molecules, which comprise gut endocrine promoters, because the sequence of DNA molecules would be expected to vary among individuals. The specification discloses various gut endocrine promoters on pages 14-15 but does not disclose any variants or functional subsequences of gut endocrine promoters embraced by the claims. There is no evidence on the record of a relationship between the structure of any gut endocrine promoter and the claimed variants or functional subsequences that would provide any reliable information about the structure of other gut endocrine promoter DNA molecules within the genus. There is no evidence on the record that the disclosed gut endocrine promoters had a known structural relationship to any of the claimed variants or subsequences embraced by the claims; the art indicated that there is variation between gut endocrine promoter DNA sequences. There is no evidence of record that would indicate that any of the claimed variants or subsequences of gut endocrine promoters even have the biological activity of a gut endocrine promoter. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by variants or subsequences of the genus, because the disclosed gut endocrine promoters are not representative of the claimed genus, which includes variants or subsequences. Consequently, since Applicant was in possession of only the disclosed gut endocrine promoters and since the art recognized variation among the species of the genus of DNA molecules that

comprise gut endocrine promoters, the disclosed promoters are not representative of the claimed variants or subsequences. Therefore, Applicant was not in possession of the genus of variants or subsequences of gut endocrine promoters as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 31-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a subject having, or at risk of having, a disorder treatable by producing a therapeutic protein in a muscosal tissue, comprising contacting muscosal tissue cells in the subject transformed with a polynucleotide comprising an expression control element in operable linkage with a nucleic acid encoding the therapeutic protein with a nutrient that induces production of the protein in an amount effective to treat the disorder, wherein the expression control element comprises a nutrient-regulatable element.

The specification discusses that the invention features methods of targeting expression of a protein of interest to endocrine cells in the

gastrointestinal tract such that a therapeutically effective amount of the protein can be secreted upon the ingestion of a nutrient that increases production of the protein. See the paragraph bridging pages 9-10. The specification discusses that the invention features a nutrient inducible system for producing a therapeutic protein in gut endocrine cells and goes on to provide prophetic teachings for implementing such a system. See pages 50-52, as well as throughout the specification. While the specification provides extensive teachings pertaining to production of a therapeutic protein, such as insulin, *in vitro* (see pages 43-45), the specification fails to provide any relevant teachings or specific guidance or working examples with regard to the production of insulin *in vivo*, by way of the claimed methods, that results in therapy or prevention of diseases, such as diabetes or obesity (see page 6 of the specification). It appears that the guidance provided by the instant specification fails to correlate the production of a therapeutic protein *in vitro* to production of a therapeutic protein *in vivo* resulting in treatment or prevention of disease. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating or preventing disease. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims are directed to methods of treating or preventing a disorder in a subject by producing a therapeutic protein in a muscosal tissue and clearly fall into the realm of gene therapy. While it should be noted that some of the claims, such as independent claim 31, are not limited to any particular disorder or

therapeutic gene, the specification has contemplated treating or preventing diseases such as type I diabetes or obesity by the *in vivo* introduction of a therapeutic gene, such as the human insulin gene, into muscosal cells of a subject, wherein the therapeutic gene is expressed in response to a nutrient but has not provided any specific guidance or working examples that correlate to treatment of any disease, particularly diabetes or obesity. Since the instant specification has failed to provide specific guidance or working examples correlating to treatment of a disease one of skill in the art could not rely on the state of the gene therapy art to treat any disease by way of the claimed methods. This is because the art of gene therapy is an unpredictable art with respect cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. These issues are discussed by two published reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the

system. Moreover, Applicant's claims do recite any particular mode of administration of a therapeutic gene or a means to target muscosal tissue with a therapeutic gene. The specification has contemplated the use of *ex vivo* methods of gene transfer for introducing a therapeutic gene particularly a gene encoding insulin, into a muscosal endocrine cell line, K cells. See pages 50-52. The specification however, has not provided any specific guidance or teachings with regard to the other modes of cell targeting or modes of administering a therapeutic gene encompassed by the claims. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art, which shows promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion

section). Verma reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). It should be noted that although the publication date of these cited references is prior to the filing date of the instant application, the issues regarding the unpredictability of gene therapy remain the same and have not be resolved by the guidance provided by the instant specification.

With regard to gene therapy for treatment or prevention of type I diabetes as contemplated by the instant specification, the state of the art of diabetes type I gene therapy suggests that while some progress has been made to date there are issues that remain, which make the treatment of diabetes type I by gene therapy unpredictable. Yoon et al (2002, Trends Mol. Med., 8(2): 62-68) discuss the recent progress made in the field of type I diabetes (insulin-dependent diabetes mellitus, IDDM) gene therapy and limitations that hamper gene therapy from effectively treating or preventing IDDM. Yoon et al suggest that a possible treatment for IDDM is the development of β-cell substitutes by introducing an

insulin-producing gene into non-β cells, which would evade the β-cell specific autoimmune attack. However, use of non-β cells for insulin production has not been feasible due to the absence of the following: an appropriate glucose-sensing system to regulate insulin gene transcription, enzymes that process proinsulin to insulin and glucose-regulatable exocytosis in the target cells. See the abstract. According to Yoon et al, an effective insulin gene transfer system is necessary for successful insulin gene therapy. Yoon goes on to discuss various viral and non-viral systems for transfer of the insulin gene (the discussion repeats some of the issues for each system addressed above, but with respect to insulin gene transfer). See pages 62-64. The major hurdle for effective insulin gene therapy, in the opinion of Yoon et al, is the lack of highly regulated biosynthesis and secretion of transgenic insulin in non-β cells. See pages 64-65. Another important problem that must be overcome for insulin gene therapy to be effective is the ability of a non-β cell to produce biologically active insulin. As discussed by Yoon et al (see pages 65-66) preproinsulin must undergo several stages of processing before biologically active insulin is produced; the problem being that most non-β cells lack the β-cell-specific endoproteases that convert proinsulin to insulin. Finally, Yoon et al stress the need to identify and utilize a target cell, having the same characteristics specific to the production of insulin. See pages 66-67. It appears that the K cell has emerged as a target cell that may *potentially* be the missing piece in the puzzle for effective insulin gene therapy because of its ability to process proinsulin to insulin. Yoon et al comments on the instant inventors' work (Cheung et al, 2000, Science, 290: 1959-1962), which,

demonstrated that transgenic mouse K cells can produce human insulin. See page 66, column 2, the 2nd full paragraph. Yoon et al concludes that an effective means of gene delivery to K cells needs to be developed for *in vivo* gene therapy [to be successful in treating IDDM]. Corbett et al (2001, Trends Endocrinol. Metabol., 12(4): 140-142) support the conclusions of Yoon et al in commenting on the instant inventors' work (Cheung et al). Corbett et al report that transgenic mouse K cells can produce human insulin and in doing so have the ability to normalize glucose homeostasis in diabetes and in response to a glucose challenge. Corbett et al suggest that K cells might be an excellent cellular target for gene therapy but at the same time reiterate Yoon et al by stating that methods for gene delivery to the gut, where K cells are normally found, have not yet been developed. Corbett et al further discusses that for gene delivery to the gut to be successful, K-cell progenitor or stem cells need to be the target of gene therapy because of the rapid rate at which gut epithelial lining cells are shed. See column 3 on page 141. *In the long term*, Corbett et al posits that gene therapeutic approaches targeting glucose responsive K cells *could* provide a novel and attractive method for the treatment of patients with IDDM. In concluding Corbett raises a final issue regarding insulin gene therapy, which is the fact that insulin is an autoantigen identified in patients with new onset of IDDM and in the non-obese diabetic (NOD) mouse model of autoimmune diabetes, from which insulin-reactive T-cell clones have been isolated. In light of such, Corbett et al cautions that K cells engineered to produce insulin could also become the targets of autoimmune-mediated destruction, an event that could

also result in gut inflammation. The instant inventors' own publication (Cheung et al) while reporting the results outlined above by Yoon and Corbett suggests that genetic engineering of gut K cells to secrete insulin *may* represent a viable mode of therapy for diabetes *in the future*. See page 1961.

In light of the above, it appears that the state of the art is suggesting that insulin gene therapy might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of insulin gene therapy raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of insulin gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating IDDM by insulin gene therapy without a reasonable expectation of success.

With regard to use of the claimed methods for treating obesity, it would appear that the issues regarding a gene transfer system to the gut, as discussed above with respect to insulin gene therapy, are also relevant when considering the contemplations of the instant specification. The specification fails to provide teachings, specific guidance, or working examples that correlate to the treatment of obesity by way of the claimed methods. Furthermore, the instant specification fails to provide the skilled artisan with guidance for targeting gut cells with a vector comprising a therapeutic gene, the expression of which could result in treatment of obesity, or with specific guidance regarding the level of expression of a therapeutic gene, such as leptin, necessary for treating or preventing

obesity. Moreover, the state of the art of obesity gene therapy is unpredictable and undeveloped. For example, Buettner et al (2000, Am. J. Physiol. Endocrinol. Metab., 278: E563-569) report "the ability of leptin administration to reverse metabolic abnormalities in the ob/ob mouse and improve insulin action in normal animals has led to the proposal that leptin may serve as an effective therapy for human obesity". Buettner et al go on to caution that before leptin can effectively be used to treat obesity a number of questions must first be answered. "First, it is not clear that increasing plasma leptin levels will be sufficient to correct the metabolic abnormalities associated with obesity, principally insulin resistance and perturbed lipid and carbohydrate metabolism. Second, leptin therapy involving multiple injections has had mixed results both in animal models of obesity and in human trials, and this suggests that alternative strategies such as sustained increases in plasma leptin should be considered." See page E566, column 2, 1st paragraph. Further, the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of leptin gene therapy raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of leptin gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating obesity by leptin gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a disease, particularly

type I diabetes or obesity, the lack of direction or guidance provided by the specification for treatment of a disease, particularly type I diabetes or obesity , the absence of working examples that correlate to the treatment of a disease, particularly type I diabetes or obesity, the unpredictable state of the art with respect to gene therapy, and in particular gene transfer *in vivo* to endocrine cells of the gut, the undeveloped state of the art pertaining to the treatment of type I diabetes or obesity by gene therapy, and the breadth of the claims directed to all diseases and cell types, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

Peter Paras
Art Unit 1632